dsDNA,
Nucleosome,
Ku,
Centromere A,
Centromere B,
Scl-70,
Pm-Scl,
RNA-Polymerases 1, 2, and 3,
Th,
Jo-1,
Mi-2,
PL7,
PL12, and
SRP.

A3 cont'd

REMARKS

The amendment to claim 1 is an incorporation of four of the specific pattern recognition methods from the Markush group of claim 3, and the amendment to claim 3 is an elimination of two of the members of the Markush group to leave the group with only three members. All other changes are editorial in nature for purposes of clarification, with no effect on scope or content. No new matter is presented by any portion of this amendment.

Claim Rejections -- 35 USC §112, First Paragraph

This rejection for lack of enablement is respectfully traversed.

The rejection states that "the specification does not associate any antigen (or antibody) with any particular disease with respect to presence (or absence) and amounts as implied by the claim." This invention does not involve the association of particular antigens or antibodies with particular diseases, and such association is neither stated in nor implied by the claims of this application. Instead, the invention resides in,

and claim 1 expressly recites, comparing a test data set to a library of reference data sets each of which has been obtained from a subject known to have a particular autoimmune disease. There is no correlation between antibodies and diseases, only between one test data set and a library of reference data sets. There is no assigning of presence, absence or amounts of any particular antibodies to any particular disease since the reference sets are already identified as to the diseases that they appear in. This is explained in the specification at page 4, in the first paragraph under the heading "Detailed Description of the Invention and Specific Embodiments."

The rejection also states that "the specification [does not] disclose how discrimination between different autoimmune diseases, particularly with those that involve overlapping autoantibodies, is to be implemented." To the contrary, the specification does indeed disclose how such discrimination is achieved. Discrimination between the various autoimmune diseases is achieved by any of the various pattern recognition methods, each of which is designed to discriminate between large sets of data, particularly data sets that overlap. Pattern recognition methods are statistical analyses, and each one is known in the art, although for other uses. Each method is summarized in the specification at page 5, line 14, through page 6, line 28. It is well settled that a patent need not teach, and preferably omits, that which is well known in the art. MPEP §2164.01.

The Peter et al. text referenced on page 7 of the specification is cited merely to indicate that the autoimmune antibodies are known to exist and that a large number of these antibodies have known antigens. Peter et al. is cited only to indicate the state of the art, and is not a disclosure of the invention or of elements, otherwise unknown, that are critical to the implementation of the invention. The incorporation of Peter et al. by reference is therefore not improper.

The examiner's characterization of principal component analysis is not consistent with the literature on this method. While principal component analysis can be used in combination with other pattern recognition methods, it can also be used as a means of pattern recognition in and of itself. Accompanying this Amendment is an

Information Disclosure Statement that includes a selection of published materials downloaded from the Internet describing principal component analysis and various types of data processing for which it can be used. These materials are:

Huang, H.-L., "Application of Principal Component Analysis to High-Resolution Infrared Measurement Compression and Retrieval," *J. Appl. Meteorology*, vol. 40, pp. 365-388 (March 2001)

Hyvarinen, A., "Principal Component Analysis," dated April 23, 1999

van Ooyen, A., abstract: "Theoretical Aspects of Pattern Analysis -- A Simple Introduction to Principal Component and Cluster Analysis," *New Approaches for the Generation and Analysis of Microbial Typing Data*, eds., Dijkshoorn, L., et al., Elsevier, Amsterdam, 2001, pp. 31-45

The Huang paper states on page 371 (left column, top line) that "PCA is a multivariate analysis technique," and concludes on page 380 (left column first sentence) that:

> "These results demonstrate that PCA, PCC, and PCR methods will be effective in processing the high volume of data provided by the new generation of instruments and in accomplishing accurate sounding profile retrieval."

The Hyvarinen paper ("Principal Component Analysis") states in the first line of text that: "Principal Component Analysis, or PCA (see [77,87]), is widely used in signal processing, statistics, and neural computing." The title of the van Ooyen paper ("Theoretical Aspects of Pattern Analysis -- A Simple Introduction to Principal Component and Cluster Analysis") clearly indicates that principal component analysis is one example of pattern recognition analysis and the text of the paper identifies principal component analysis and cluster analysis as two distinct approaches to pattern recognition. These disclosures demonstrate the recognition among those skilled in the art of principal component analysis as a statistical method and that it can indeed be used as a means of pattern recognition.

The three papers listed above also show that the adaptation and use of principal component analysis (as one example of a pattern recognition system) is well

within the routine skill of those familiar with statistical analysis and data processing. Further papers listed in the IDS show that other methods recited in Applicants' claims are also pattern recognition methods. The Assadi document entitled "A Basic Introduction to Pattern Recognition" lists various methods, including probabilistic decision making and k-nearest neighbor as pattern recognition methods. The Tobin, K.W., et al. paper entitled "Adaptation of the Fuzzy K-Nearest Neighbor Classifier for Manufacturing Automation" likewise lists k-nearest neighbor as a pattern recognition method. The Castelli, V., et al. course summary entitled "EE 6880 Special Topics in Signal Processing -- Statistical Pattern Recognition" lists both Bayesian decision theory and networks and k-nearest neighbor as pattern recognition methods. These references are not a comprehensive literature survey but merely the result of a quick key-word search on the Internet. Many other pieces of literature exist, both on the Internet and elsewhere, addressing these particular methods and other methods within the scope of the invention and characterizing them as pattern recognition methods.

It is true that pattern recognition methods need to be adapted for use in any particular application, but these literature documents demonstrate that such adaptation is within the routine skill of the experienced data statistician. In the present invention, the instant specification explains that the data to be used and the attributes as well are simply the presence and amounts of known autoimmune antibodies, the analysis method and algorithms are known characteristics of each pattern recognition method and readily adaptable by anyone skilled in the use of these methods. Furthermore, the composition of the training set and the test sets are known autoimmune antibodies. The specification explains this thoroughly and adequately, citing a large number of examples of autoimmune antibodies. The specification is not a mere "invitation to experiment" as it is characterized by the Office Action. The specification is a teaching that when combined with the existing knowledge and the routine level of skill among data processors and statisticians provides a fully enabling disclosure to support the claims. Accordingly, the rejection of the claims under 35 USC §112, first paragraph, is respectfully traversed.

Claim Rejections -- 35 USC §112, Second Paragraph

This rejection for indefiniteness is traversed as well.

The examiner has questioned the symptoms indicated by the phrase "suspected of suffering from an otherwise unidentified systemic autoimmune disease" appearing in Applicants' claim 1. The meaning of this phrase is not unclear -- symptoms that raise the suspicion of an autoimmune disease are well known to those skilled in the art. Evidence of this is found in the various websites of the National Institute of Allergies and Infectious Diseases (of the National Institutes of Health), downloaded pages of which are included in the enclosed IDS. The page entitled "How are Autoimmune Diseases Diagnosed?" for example refers to skeletal symptoms such as joint pain and positive but nonspecific laboratory tests. The pages entitled "What Are Some Examples of Autoimmune Diseases?" cites such symptoms as pain, swelling, and stiffness of the joints (rheumatoid arthritis), fatigue, frequent urination, increased thirst, and sudden confusion (diabetes), diarrhea, nausea, vomiting, abdominal cramps (inflammatory bowel diseases), fatigue, rashes, and joint pain (systemic lupus erythmatosus), and others. The downloaded document entitled "Phar 441 Immunology" lists the major symptoms of each of the most common autoimmune diseases. These disclosures indicate considerable overlapping of symptoms among the different autoimmune diseases and they cite various symptoms or types of symptoms that raise a suspicion that the patient is suffering from an autoimmune disease but fail to confirm which particular autoimmune disease is present. No skilled artisan familiar with autoimmune diseases will have any difficulty knowing the scope and meaning of the phrase in Applicants' claim 1.

The objection to claim 2 is hopefully obviated by the amendment herein. Note also that the preamble of claim 1 recites "*an* otherwise unidentified systemic autoimmune disease" which is patent parlance means "*one or more*" such diseases.

> "As the district court correctly noted, 'a first clock signal' does not require a *single* clock signal ... the article 'a' in 'a first clock signal' generally suggests one or more clocks." See *Crystal Semiconductor Corp. v. TriTech Microelectronics International Inc.*, 57 USPQ 2d 1953 at 1960 (Fed. Cir. 2001).

Claim 2 further limits claim 1 by restricting to two or more diseases, eliminating patients with only one disease. Foreknowledge of the presence of two or more diseases is not required since the claimed method itself will indicate whether or not there are two ore more such diseases. Nor is a forenowledge of the particular diseases required since the method recited in the claim includes the determination of which two diseases the patient is suffering from if in fact the determination indicates that two diseases are present.

Regarding the objection to claim 3, pattern recognition methods are indeed a type of statistical analysis, as explained above and demonstrated in the literature on the subject.

The objections to claims 7, 8, and 11 are fully addressed by the amendment herein.

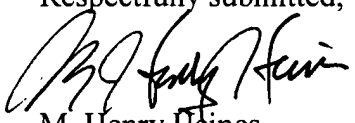
Claim Rejections -- 35 USC §102

The recitation of neural network analysis has been removed from the claims, and accordingly this rejection should be withdrawn, since the disclosure in Grus et al. is limited to neural network analysis.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and reconsideration of the application is respectfully requested. Should any matters remain that can be resolved by a conference with Applicants' attorney, the examiner is encouraged to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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APPENDIX A

AMENDED PARAGRAPH ON PAGE 5, LINES 23-28 WITH MARKINGS SHOWING CHANGE

Principal component analysis is a multivariate technique for reducing matrices of data to their lowest dimensionality by use of orthogonal factor space. According to this technique, the training set is processed to identify the number of principal components. This information is then used to model the **patient** [patent] test data using such techniques are target transformations or curve fitting. Neither the principal component nor the neural network analyses are suitable for the detection of two diseases.

AMENDED PARAGRAPH ON PAGE 7, LINE 3, TO PAGE 8, LINE 5 WITH MARKINGS SHOWING CHANGE

The test data used in the present invention are values that are proportional to, or otherwise representative of, the levels of various antibodies that are associated to various degrees with systemic autoimmune diseases. Currently, over 100 antibodies are known to be expressed in autoimmune diseases. Examples are listed in Peter, J.B., et al., *Autoantibodies*, Elsevier Science B.V., Amsterdam (1996), the contents of which are incorporated herein by reference. The antigens to many of these antibodies are commercially available, while the antigens to others are readily synthesized based on descriptions of them that are available in the literature. Some of the sources of these antigens are BiosPacific, of Emeryville, California, USA; Immunovision, of Springdale, Arkansas, USA; and KMI Diagnostics, Inc., of Minneapolis, Minnesota, USA. Examples of the antibodies that are expressed in autoimmune diseases, identified by the antigens to which they bind in an immunoassay, are listed below:

SSA 60

[SSA 60]

SSA 52

SSB 48

Sm BB'

Sm D1

RNP 68

RNP A

RNP C

Fibrillarin

Riboproteins P0, P1, and P2

dsDNA

Nucleosome

Ku

Centromere A

Centromere B

Scl-70

Pm-Scl

RNA-Polymerases 1, 2, and 3

Th

Jo-1

Mi-2

PL7

PL12

SRP

APPENDIX B

AMENDED CLAIMS WITH MARKINGS SHOWING CHANGES

1. (amended) A method for the identification of a systemic autoimmune disease in a test subject suspected of suffering from an otherwise unidentified systemic autoimmune disease selected from the group consisting of systemic lupus erythmatosus, scleroderma, Sjögren's syndrome, polymyositis, dermatomyositis, CREST, and mixed connective tissue disease, said method comprising:

(a) analyzing a single biological sample from said test subject for the presence and amounts of a plurality of autoantibodies to produce a test data set;

(b) comparing said test data set to a library of reference data sets, each reference data set obtained from a biological sample of a reference subject known to have a systemic autoimmune disease of known identity; and

(c) applying pattern recognition means **selected from the group consisting of k-nearest neighbor analysis, multi-linear regression analysis, Bayesian probabilistic reasoning, and principal component analysis** to produce a statistically derived decision indicating which systemic autoimmune disease said test subject is suffering from.

2. (amended) A method in accordance with claim 1 in which said test subject is suffering from two **otherwise unidentified** systemic autoimmune diseases, and step (c) comprises applying pattern recognition means to produce a statistically derived decision indicating which two systemic autoimmune diseases said test subject is suffering from.

3. (amended) A method in accordance with claim 1 in which said pattern recognition means is a member selected from the group consisting of k-nearest neighbor analysis, multi-linear regression analysis, **and** Bayesian probabilistic reasoning[,neural network analysis, and principal component analysis].

7. (amended) A method in accordance with claim **1** in which said plurality of autoantibodies comprises antibodies to at least fifteen of the following antigens:

SSA 60_2

[SSA 60]

SSA 52_2

SSB 48_2

Sm BB'_2

Sm $D1_2$

RNP 68_2

RNP A_2

RNP C_2

$Fibrillarin_2$

Riboproteins P0, P1, and $P2_2$

$dsDNA_2$

$Nucleosome_2$

Ku_2

Centromere A_2

Centromere B_2

Scl-70_2

Pm-Scl_2

RNA-Polymerases 1, 2, and 3_2

Th_2

Jo-1_2

Mi-2_2

$PL7_2$

$PL12_2$ **and**

SRP.

8. (amended) A method in accordance with claim **1** in which said plurality of autoantibodies comprises antibodies to each of the following antigens:

SSA 60,
[SSA 60]
SSA 52,
SSB 48,
Sm BB',
Sm D1,
RNP 68,
RNP A,
RNP C,
Fibrillarin,
Riboproteins P0, P1, and P2,
dsDNA,
Nucleosome,
Ku,
Centromere A,
Centromere B,
Scl-70,
Pm-Scl,
RNA-Polymerases 1, 2, and 3,
Th,
Jo-1,
Mi-2,
PL7,
PL12, **and**
SRP.